Universidad de Navarra

Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Research Project Proposal

Academic year 2022-2023

Project Nº 51 ASIGNADO

Title: LEISHMANICIDAL ACTIVITIES OF REPURPOSED COMPOUNDS.

Department/ Laboratory

ISTUN Instituto de Salud Tropical Universidad de Navarra. Dpto. de Microbiología y Parasitología

Director 1 PAUL NGUEWA, panguewa@unav.es

Director 2 Celia Fernández Rubio

Summary

Leishmaniasis, one of the 20 neglected tropical diseases recognized by the World Health Organization (WHO), is caused by the protozoan parasites of the genus *Leishmania*. It exhibits three main clinical forms: visceral, cutaneous, and mucocutaneous leishmaniasis. Considering tropical infections impact and disease burdens, leishmaniasis ranks second in mortality and fourth in morbidity. WHO estimates that Leishmaniasis is prevalent in 98 countries on five continents, and exhibits an incidence of 1.3 million new cases annually, of which 300,000 are visceral and 1 million are cutaneous or mucocutaneous.

It is well known that generic pentavalent antimonials have been the essential chemotherapy agents against this pathology. Sodium stibogluconate and meglumine antimoniate are alternatives treatment. Other treatments, such as amphotericin B and miltefosine offer a higher efficacy but a costlier option to pentavalent antimonials. Some broad-spectrum antimicrobials (e.g., paromomycin and pentamidine) show some benefit in the treatment of this disease, especially when used in conjunction with other drugs regimen. Nevertheless, all these pharmacological compounds raise severe side effects without the confidence of complete healing and currently various Leishmania strains have developed resistance against these drugs. Due to the lack of an effective vaccine, existing means for disease control are limited to the management of vector and reservoir hosts in order to reduce transmission, and treatment by chemotherapeutic agents. Therefore, the search and validation of new therapeutic targets allowing the development of innovative drugs have become a worldwide priority. Our group has discovered and validated LmJPES, Lmj_04_BRCT domain as novel therapeutic targets in *Leishmania* spp. Their structures had been explored using homology modeling, virtual screening, and molecular dynamics studies. Several candidate compounds were identified. This work will present the *in vitro* validation using promastigotes of *Leishmania major*, *L. amazonensis*, and

L. infantum, as well as primary mouse macrophages infected with *L. major* though MTT assays. The activity of drug candidates will be also tested on amastigotes after *in vitro* infection of macrophages. On the other hand, by real-time PCR, we will study the expression levels of genes from parasites treated with the most promising candidates. *Leishmania* genes involved in processes such as cell cycle, infectivity, treatment response… will be analysed.

Methodology will include parasite culture; cell viability assays; *In vitro* infection of macrophages; cell stain; microscopy; and different Molecular techniques (: nucleic acids extraction from biological samples, conventional PCR, Real-time PCR).

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?

yes	X
no	